REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Claim Amendments

Claim 20 is amended to recite methods comprising administering an amount of a composition containing full length NY-ESO-1 protein and a saponin based adjuvant that is sufficient to reduce the risk of relapse. This subject matter is supported by the preamble of previous claim 1, and throughout the specification as filed. For example, Example 6 discusses the ability of the claimed methods to reduce the risk of relapse. Claim 20 also is amended to address the objection set forth at page 9 of the Office Action.

Applicant respectfully urges entry of this amendment after final because it is not believed to raise any new issues or require a further search. To the contrary, the amendment merely recites in the body of the claim aspects previously recited in the preamble, and previously considered by the Examiner, as reflected in the Office Action.

Upon entry of this amendment, claims 20-22, 25, 26 and 34-37 will remain pending. These claims are presented for reconsideration.

II. Claims Under Examination

Applicant notes with appreciation the indication that examination is extended to the subject matter of claim 34, such that claims 20-22, 25, 26 and 34-37 are under examination.

III. § 102 Rejection

The claims are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Cebon *et al.*, *Proc. Amer. Soc. Clin. Oncol.* 21, abstract 86 (June 2002) ("Cebon"). Office Action, at 2-4. Applicant respectfully traverses.

The Examiner cites Cebon for teaching the administration of full-length NY-ESO-1 protein and ISCOM adjuvant to patients with NY-ESO-1 positive tumors and minimum

residual disease, in order to evaluate safety and immunogenicity. Office Action, page 2. The Examiner finds that the amounts of NY-ESO-1 protein used (10, 30 or 100 μg) and that the amount of ISCOM used also appears to be within the scope of the claims. Office Action, pages 2-3. Thus, the Examiner asserts that "the protocol used by Cebon et al is the same as that disclosed in the instant specification." Office Action, page 3.

At the outset Applicant questions the basis for the finding that "it appears that the amount of ISCOM in the composition with NY-ESO-1 at least for the 100 μg NY-ESO-1 administration is equal in amount." Office Action, page 3. This finding is based on the assertion that Cebon teaches "that the control amount of ISCOM administered was 100 μg." *Id.* Applicant is unable to find such a teaching in the Cebon abstract or slides. The abstract and slides do indicate that one patient group "received 100 μg NY-ESO-1 protein alone," but there is no mention of a patient group that received ISCOM alone. Moreover, although the slides refer to "placebo" patients, neither the slides nor the abstract disclose the placebo formulation. The Examiner cannot assume that the placebo patients were administered ISCOM alone, let alone that they were administered 100 μg ISCOM.

Given that Cebon does not, in fact, disclose the amount of ISCOM used, it does not teach every aspect of the claimed invention as required for a § 102 rejection. For example, the instant claims recite "administering . . . an amount of a composition containing full length NY-ESO-1 protein and a saponin based adjuvant, sufficient to induce an antibody response to NY-ESO-1 in said subject and reduce the risk of relapse." Cebon does not provide any guidance on the amount of saponin based adjuvant that is sufficient to achieve the recited effects.

Cebon's failure to disclose the amount of ISCOM used also means that it does not enable the skilled artisan to carry out the methods described in Cebon, let alone the claimed methods. It is well-established law that "[i]n order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make [or use] the invention without undue experimentation. . . . In other words, the prior art must enable the claimed invention." *Impax Labs. V. Aventis Pharmaceuticals, Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008) (internal citations omitted). As set forth in *In re Gleave*, 560 F.3d 1331, 1335 (Fed.

Cir. 2009), "[t]he only way one can show that a reference enables the method is to show that a person of ordinary skill would know how to use—in other words, to practice or to carry out—the method." Because the Cebon abstract and slides do not provide any information on the amount of ISCOM to use, they do not enable the skilled artisan to carry out even their own methods, and therefore cannot support a §102 rejection.

The Examiner recognizes that Cebon does not "correlate the clinical response in their study" or teach that the method is effective to reduce the risk of relapse, as recited in the claims. See, e.g., Office Action, page 3. Nevertheless, the Examiner finds that Cebon anticipates the claimed methods because the patient population treated by Cebon appears to coincide with patient populations at risk of relapse (citing paragraph [0022] of the instant specification) and that reduction of the risk of relapse "appears to be an inherent property" of the method. Applicant respectfully disagree.

First, as noted above, the assertion of inherency is based on the assumption that Cebon discloses the use of amounts of ISCOM within the scope of the claims. Because Cebon does not provide any teachings on effective amounts of ISCOM, Cebon fails as an anticipatory reference on this basis alone.

Moreover, although the Office Action cites *Bristol-Myers Squibb Co. V. Ben Venue Labs.*, 58 USPQ2d 1508 (Fed. Cir. 2001), in support of the rejection, this case does not govern here for several reasons. Claim 1 at issue in *Bristol-Myers* recited:

> A method for reducing hematologic toxicity in a cancer patient undergoing Taxol treatment comprising parenterally administering to said patient an antineoplastically effective amount of about 135-175 mg/m 2 taxol over a period of about three hours.

Id. at 1510 (emphasis added). The court determined that the preamble was a "non-limiting" expression of purpose that was independent from the body of the claim. *Id.* at 1513. The court determined that the "antineoplastically effective amount" was secondary to the recited amount, and could not distinguish the prior art because it was added "voluntarily" after the claim already had been allowed. *Id.*

In contrast, the instant claim language regarding reducing the risk of relapse should be accorded patentable weight because it is recited in both the preamble and the body of the claim, and is being relied upon to distinguish Cebon. For example, in *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 811 (Fed. Cir. 2002), the Federal Circuit explained that "[b]y virtue of its inclusion in the body of [the claim], this phrase limits [the claim."

This difference in claim construction leads to a different result in the anticipation analysis. While the court in *Bristol-Myers* found anticipation by a prior art disclosure that "performed all of the claimed steps at dosage levels that anticipate those in the claims," key to this finding was the claim construction determination "that the claims only require the administration of specific amounts of paclitaxel and not the achievement of a particular result." *Id.* at 1515. Here, where Cebon does not disclose the amount of ISCOM administered and where the body of independent claim 20 recites the particular result of reducing the risk of relapse, *Bristol-Myers* does not govern the anticipation analysis.

Moreover, while the court in *Bristol-Myers* stated that "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent," *id.* at 1514, this principle does not apply here, because Cebon did not administer NY-ESO-1 protein and ISCOM adjuvant for "the same purpose" recited in the instant claims. As recognized in the Office Action, Cebon was evaluating the administered composition for safety and immunogenicity, with a plan for future assessment of "clinical response." Cebon was not administering the NY-ESO-1 protein and ISCOM adjuvant in order to reduce the risk of relapse in its subjects, and provides no teaching, suggestion or expectation of success in being able to do so.

Finally, again, Cebon does not teach the administration of amounts of NY-ESO-1 protein and saponin based adjuvant sufficient to reduce the risk of relapse, as recited in the instant claims, because Cebon does not provide any teaching of the amounts of ISCOM it used, let alone amounts that would be sufficient to reduce the risk of relapse.

For at least these reasons, Applicant respectfully urges reconsideration and withdrawal of the anticipation rejection based on Cebon.

IV. § 103 Rejections

The claims are rejected under 35 U.S.C. § 103 for allegedly being obvious in view of (A) WO 98/14464 in view of Batchu (2003) and WO 03/076455; (B) WO 98/14464, Batchu, and WO 03/076455, further in view of Jager (2000) and U.S. 6,506,386; and (C) Cebon, Jager, WO 03/076455 and "an admission in the specification." Applicant addresses these rejections in turn below.

A. WO 98/14464, Batchu (2003) & WO 03/076455

Claims 20-22, 34 and 35 are rejected over the combination of WO 98/14464, Batchu and WO 03/076455. Applicant respectfully traverses this rejection.

WO 98/14464 is cited for teaching the use of NY-ESO-1 antigen with a saponin-based adjuvant to treat cancer. This reference focuses on the identification of the NY-ESO-1 antigen, including the isolation of a gene encoding it, and the expression, purification and analysis of the protein. As noted by the Examiner, WO 98/14464 contemplates therapeutic uses of the protein, and mentions the use of adjuvants such as saponins, but the reference does not provide any specific guidance in this regard. Importantly, as recognized in the Office Action, WO 98/14464 provides no indication that a composition containing full length NY-ESO-1 protein and a saponin based adjuvant would be useful to reduce the risk of relapse of an NY-ESO-1 expressing cancer. The secondary references, Batchu and WO 03/076455, fail to remedy this deficiency.

WO 03/076455 is cited for teaching various saponin-based adjuvants and their administration by different routes. This reference is directed to compositions that induce antibodies that bind to a specific site on a protein associated with Alzheimer's disease, and thus is of little relevance to the claimed invention.

It is Batchu that is cited for teaching that "NY-ESO-1/adjuvant based therapies . . . can be used . . . to reduce the risk of relapse," but Batchu does not provide such a teaching.

Batchu is directed to the generation of NY-ESO-1 transduced dendritic cells (DCs) for use in DC-based immunotherapy. While Batchu notes that immunotherapeutic approaches using modfied DCs are being ***investigated*** to prevent relapse of aggressive myeloma after chemotherapy ("Discussion," page 1341), Batchu does not teach that its transduced DCs are in fact useful to prevent relapse. Moreover, Batchu includes only *in vitro* data, and therefore provides no clinical data showing the prevention of relapse. Finally, Batchu provides no indication that a composition comprising NY-ESO-1 and a saponin based adjuvant, rather than NY-ESO-1-modified DCs, would be useful to prevent relapse.

Thus, the combination of WO 98/14464, Batchu and WO 03/076455 does not provide the skilled artisan with any reasonable expectation of success in being able to reduce the risk of relapse by administering a composition containing full length NY-ESO-1 protein and a saponin based adjuvant, as recited in the instant claims. Accordingly, this obviousness rejection is improper and should be withdrawn.

B. WO 98/14464, Batchu, WO 03/076455, Jager and U.S. 6,506,386

Claims 25, 26, 36 and 37 are rejected over the combination of WO 98/14464, Batchu WO 03/076455, Jager and U.S. 6,506,386. Applicant respectfully traverses this rejection.

This rejection is based on the assumption that WO 98/14464, Batchu, and WO 03/076455 render obvious the method recited in independent claim 20. As shown above however, that is not the case. Moreover, combining those references with Jager and U.S. 6,506,386 likewise fails to render obvious the claimed invention.

Jager is directed to the use of NY-ESO-1 peptides in immunotherapeutic methods. The Office Action cites Jager's use of 100 μg doses of peptide and its discussion of disease "stabilization." However, the Examiner must appreciate that slowing disease progression is hardly equivalent to preventing relapse. To the contrary, Jager reports that 4/5 responsive patients developed additional lesions after vaccination, and were removed from its immunization program. Jager, page 12201, col. 2. Thus, Jager does not provide any indication that its peptides are useful to prevent relapse.

U.S. 6,506,386 is cited for teaching suitable dosages for antigen plus ISCOM compositions. This reference does not mention NY-ESO-1/ISCOM compositions, or suggest that any amount of such a composition would be useful to reduce the risk of relapse of an NY-ESO-1 expressing cancer. Thus, it is largely irrelevant to the patentability of the claimed invention.

For at least the foregoing reasons, the combination of WO 98/14464, Batchu, WO 03/076455, Jager and U.S. 6,506,386 does not render obvious the claimed methods. Accordingly, Applicant respectfully urges reconsideration and withdrawal of this § 103 rejection.

C. Cebon, Jager, WO 03/076455 & "the specification"

Claims 20-22. 25. 26 and 34-37 are rejected over the combination of Cebon, Jager, WO 03/076455, Jager and an alleged "admission" in the specification regarding the patient population studied to evaluate the risk of relapse. Applicant respectfully traverses this rejection.

As reflected at pages 8-9 of the Office Action, this rejection is based on the same misinterpretation of Cebon and erroneous claim construction as the § 102 rejection rebutted above. Thus, the rejection is founded on the incorrect assumption that Cebon teaches the use of 100 μg ISCOM with 100 μg NY-ESO-1 protein, which it does not, and the resulting incorrect conclusion that Cebon teaches "the same protocol" as recited in the claims. As shown above, Cebon does not provide any guidance on the amount of ISCOM to use, let alone indicate that any amount of NY-ESO-1 protein and ISCOM would be effective to reduce the risk of relapse, as claimed. The rejection also improperly ignores the claim language relating to reducing the risk of relapse. When Cebon is read without hindsight and all of the claim language is given weight, it is clear that Cebon does not teach or suggest the claimed methods.

Combining Cebon with Jager and WO 03/076455 fails to remedy its deficiencies. As shown above, Jager does not provide any expectation of success with regard to the ability to reduce the risk of relapse. Indeed, no combination of Cebon, Jager and WO 03/076455

provides any indication that any amount of NY-ESO-1 protein and saponin-based adjuvant would be effective to reduce the risk of relapse. Thus, this combination of references fails to establish a prima facie case of obviousness. Applicant therefore respectfully urges reconsideration and withdrawal of this § 103 rejection.

V. Unexpected Results

Even if the cited references did some how make out a prima facie case of obviousness, it would be overcome by the unexpected results achieved by the claimed methods. As discussed in Applicant's previous response, two sets of data of record provide evidence of the unexpected results associated with the methods of the present invention.

Specifically, Example 6 of the specification shows that out of a total of ***nineteen*** patients who were treated with a composition as recited in the pending claims (NY-ESO-1 + ISCOM adjuvant, dose A, B & C), only ***two*** had relapsed after a median follow-up of 748 days. *See* paragraph [0048]. In contrast, ***six out of sixteen*** antigen-only treated patients relapsed, and ***five out of seven*** placebo-treated patients relapsed. *See* paragraph [0048].

The patients were followed for an additional year, and the time to relapse of patients receiving NY-ESO-1/ISCOM showed a significant difference (p=0.02) as compared to placebo patients. *See* Figure 7 and paragraph [0049]. After one year of additional follow-up, a total of five of nineteen subjects treated with a composition as claimed had relapsed, seven of sixteen antigen-only treated patients relapsed, and relapse in the placebo group remained at five out of seven. *See* paragraph [0050]. Such an effect on ***relapse*** could not have been expected from Cebon.

The further follow-up study reported in the Nicholaou manuscript submitted previously provides additional evidence that the claimed methods unexpectedly reduce the risk of relapse, with superior relapse-free survival observed ***three years*** post-vaccination. In particular, Nicholaou reports that 10 of 14 patients who had been vaccinated in accordance with the invention (NY-ESO-1 + ISCOMATRIX) exhibited ***persistent*** immunity, while only 3 of 14 who had been vaccinated with antigen alone or placebo exhibited long term immunity. *See* Nicholaou at 3. As noted at page 14 of Nicholaou, there "appeared to be a

highly significant reduction in relapse rates in those patients who received vaccine with ISCOMATRIX® adjuvant, the same group that had the best immune persistence."

Because none of the cited references teach or suggest a method for preventing relapse of NY-ESO-1-expressing cancer, nor indicate that the claimed methods would achieve such dramatic, long-term, beneficial results in the context of preventing relapse, the results reported in the instant application and Nicholaou are evidence of unexpected results that further support patentability.

The Office Action dismisses this evidence as applied to the § 102 rejection because "evidence of secondary considerations . . . is irrelevant" under § 102. As shown above, however, Cebon does not, in fact, anticipate the claimed methods. Thus, the evidence of unexpected results is germane to the rejections based on Cebon.

The Office Action also attempts to discredit the relevance of the unexpected results to the pending claims because "the claims do not recite that the method prevents relapse as alleged by Applicant; rather, the claims recite that the method reduces the risk of relapse." Office Action, page 9. Clearly the Examiner must appreciate that a method that prevents relapse in, for example, 17/19 patients (Example 6), reduces the risk of relapse for treated patients generally. Thus, Applicant does not understand the rationale behind this assertion.

The Office Action also ignores the evidence because Cebon's protocol allegedly "is the same protocol as Applicant's protocol." As set forth above, however, Cebon does not describe or enable a method within the scope of the claims. Moreover, to the extent that Cebon is relied upon in an obviousness rejection, the evidence is indeed probative as to patentability.

The only document of record that describes and enables a method of reducing the risk of relapse of NY-ESO-1-expressing cancer is the instant application. The efficacy of the invention in this regard, as evidenced by the human clinical trial data reported in the specification and Nicholaou manuscript, is both surprising and unexpected in view of the cited references. Indeed, the results achieved with the present invention are striking

compared to the results reported by Jager, where even the initially responsive patients developed additional lesions after vaccination.

For at least these reasons, Applicant respectfully urges reconsideration and withdrawal of the obviousness rejections.

Conclusion

Applicant believes that the present application is now in condition for allowance, and favorable reconsideration thereof is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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